Classification of and risk factors for hematologic complications in a French national cohort of 102 patients with Shwachman-Diamond syndrome

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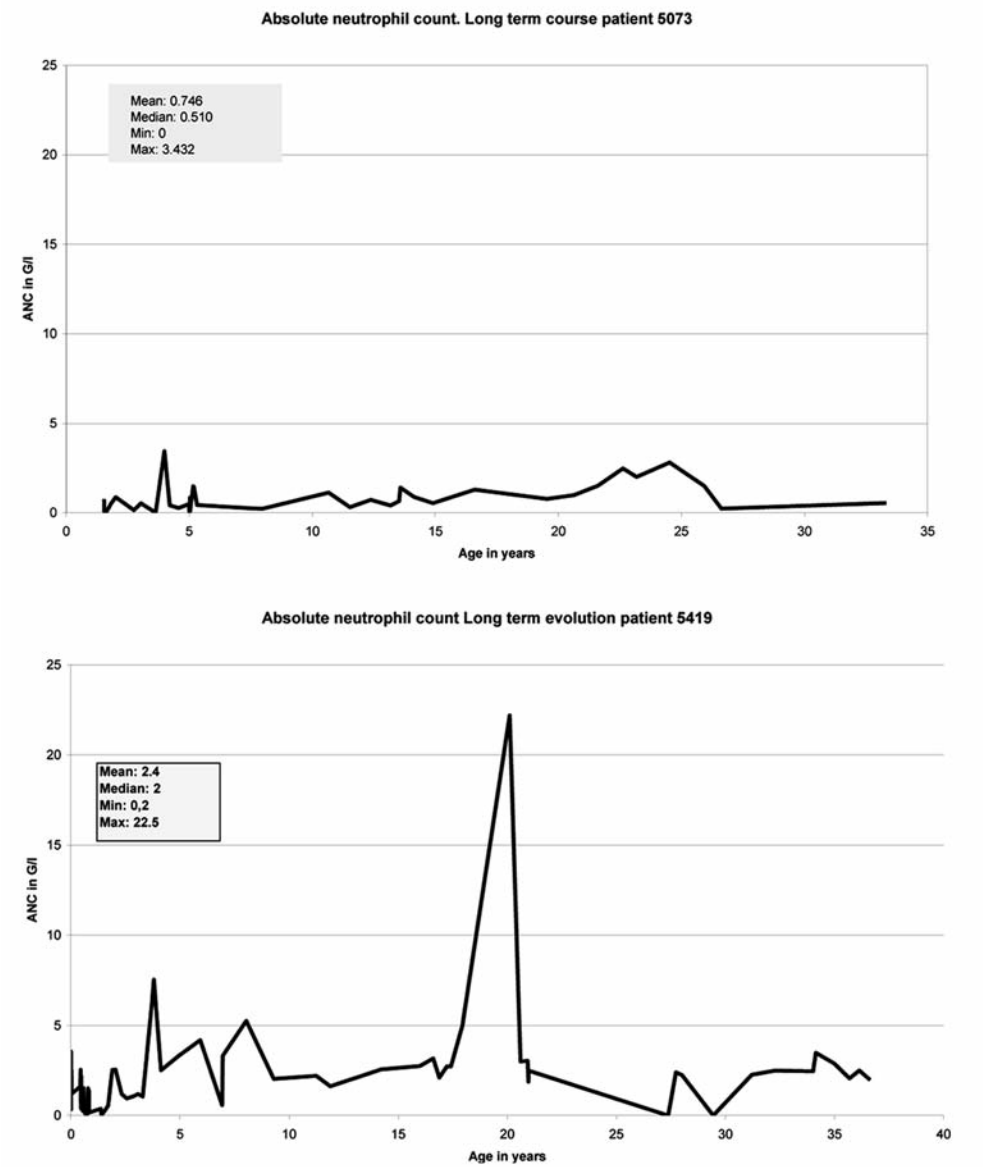
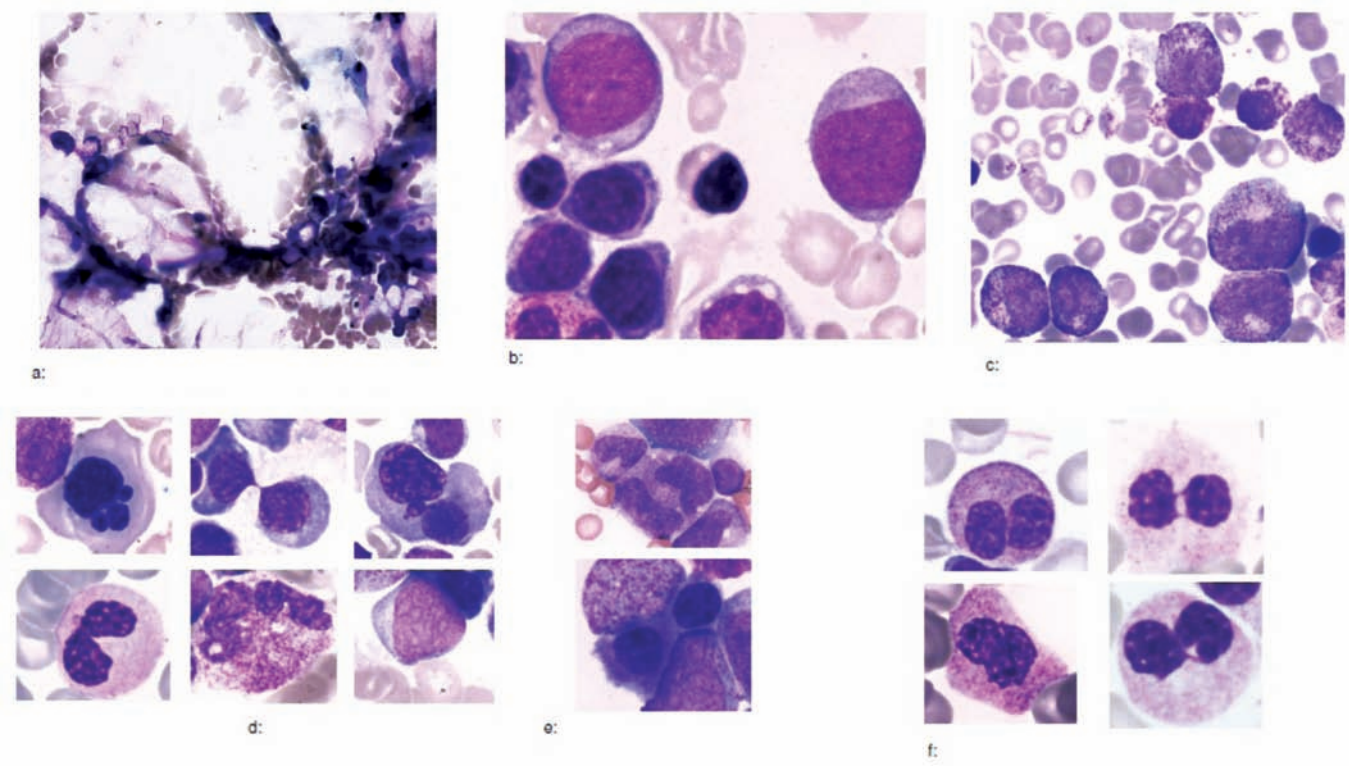
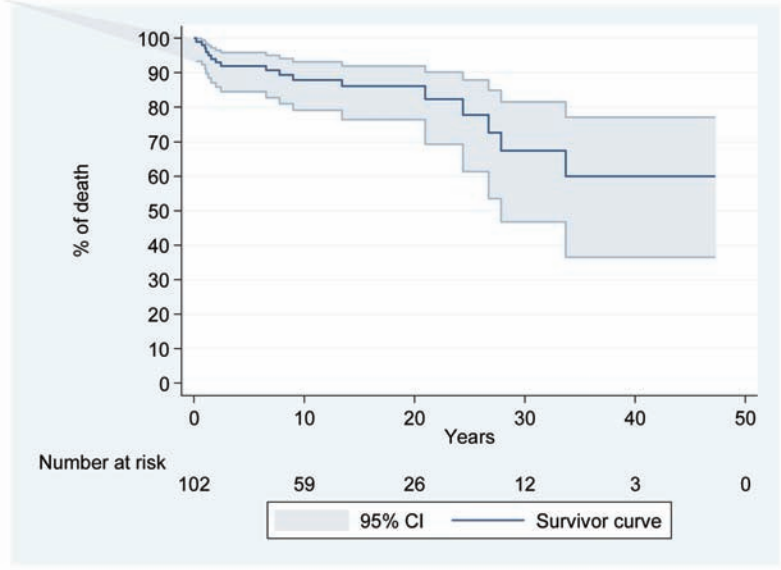


Online Supplementary Figure S1. Long-term course of routine absolute neutrophil counts in two unrelated patients bearing the same mutation, p.Lys62X p.Cys84fs.



Online Supplementary Figure S2. a: Marrow smear of a patient with Shwachman-Diamond syndrome complicated by bone marrow aplasia: poor cellularity, fat cells and mast cells. b: Marrow smear of a patient with Shwachman-Diamond syndrome complicated by acute erythroid leukemia (FAB AML 6). c: Transient not clonal SC with granulopoiesis maturation arrest. d: Marrow smear of a patient with Shwachman-Diamond syndrome complicated by cytopenia and monosomy 7 (RAEB-1). Top panel: dyserythropoiesis: karyorrhexis, multinuclearity, internuclear bridging, megaloblastoid changes. Lower panel: dysgranulopoiesis: nuclear hypolobulation, cytoplasmic hypogranularity, dual nuclear and blast e: Marrow smear in a patient with Shwachman-Diamond syndrome transient severe cytopenia with transient dysmyelopoietic features Top: dual nuclear Bottom: micromegakaryocytes with non-lobulated nuclei. f: Neutrophils on marrows smears from three patients with Shwachman-Diamond syndrome showing condensed chromatin and nuclear hyposegmentation and from one control. For each bone marrow, the proportion of neutrophils with condensed chromatin and nuclear hyposegmentation was counted. Top left: example in a patient with SC but non-malignant (mean: 34%) Top right: example in a patient without SC with cytogenetic abnormality (mean: 26%). Bottom: example in a patient with SDS without SC and without cytogenetic abnormalities (mean: 20%). Bottom right: control without SDS (mean: 4%).



Online Supplementary Figure S3. Kaplan-Meier plot showing the overall survival of the cohort of 102 patients. The time is expressed in years since birth.

Online Supplementary Table S1. Detailed description of the patients with hematologic complications, sorted by type of complication malignant: severe cytopenia, non-malignant, severe cytopenia, cytogenetic clone without severe cytopenia, transient severe cytopenia.

UPN	*SBDS* Genotype	Age*	Bone marrow cytology review	Bone marrow karyotype	Follow-up after the event (years)	Outcome (alive/HSCT/ cause of death)
Malignant SC						
5617	p.[Lys62X]+[Cys84fs]	2.5	AML with MDS related changes FAB type AML2	Monosomy 7	0.3	Death / no HSCT
5057	p.[Lys62X]+[Cys84fs]	26.3	AML with MDS related changes FAB type AML2	43,XY,-5,-7,-13,-16,-18,-20, +3mar[5] /51,XY,+1,-5,-7, +10,+10+21,+3mar[2] / 46,XY,del(20)(q11q13)[2]	0.5	Death / AML / no HSCT
5081	p.[Lys62X]+[Cys84fs]	27.2	AML with MDS related changes FAB type AML4	45, XX,add(1)(p11),-7,add(14) (q32),add(21)(q22)[20]	0.58	Death / HSCT / viral infection after HSCT
5073	p.[Lys62X]+[Cys84fs]	32.4	AML with MDS related changes FAB type AML6	41-46,XY,-5,-7,-15,-16,-19,+der(3) (?),+der(6)(?),del(13)(q13q33), der(20)(?),+r(?),+mar1, +mar2 [cp31]	1.29	Death / AML/ no HSCT
5253	p.[Cys84fs]+c.[290-1G>A]	7.3	AML with MDS related changes FAB type AML6	45,XY,del(5)(q ?q?),add(9)(q ?), +11,add(17)(p ?),-20,+22	0.42	Death / HSCT / viral infections after HSCT
5038	p.[Lys62X]+[?]	19.1	AML with MDS related changes FAB type AML6	46,XY[1]/45,XY,del(5)(q15q33), -7,+?mar[1]/44,XY,der(3)t(3;6)(?;?), del(5)(q?q?),-6,-7[19]	1.9	Death/ HSCT / death related to MDS relapse
5023	p.[Lys62X]+[Cys84fs]	22.9	AML with MDS related changes FAB type AML0	46,XY,add(15)(p?)/44,idem,-20,-21, -22,+mar[20]/46,XY[3]	1.41	Death / no HSCT
5117	p.[Lys62X]+[Cys84fs]	7.6	Refractory cytopenia with multilineage dysplasia	46,XY,del(1)(p36),t(3;21)(q26;q11), del(5)(q21q24),del(7)(q21q35), +del(8)(p21),-18[15]/46,XY[10]	1.36	Death / HSCT / death related to MDS relapse
5082	p.[Cys84fs]+ [Gln94_Val95del]	15.9	Refractory cytopenia with multilineage dysplasia	Isochromosome 7q	12.8	Alive / HSCT
Non-malignant SC followed by malignant SC						
5737	p.[Cys84fs]+c. [129-71_140del83]	0.1	Hypoplastic	No abnormality	1.5	Death / no HSCT – supportive care
		1.1	MDS (RAEB 1)	Monosomy 7	0.43	Death after HSCT / toxicities of HSCT Cond. regimen
5208	p.[Lys62X]+[Cys84fs]	0.1	Hypoplastic granulopoietic maturation arrest	No abnormality	1.01	Death / secondary MDS 0.5 years after initial event
		0.4	Refractory cytopenia with multilineage dysplasia	46,XY,i(7)(q10)[10]/46,XY[10]	0.57	Death from MDS / no HSCT
5437	p.[Cys84fs]+[Arg169Leu]	0.2	Hypoplastic granulopoietic maturation arrest	No abnormality	6.30	Death / no HSCT / secondary AML 6 years after initial event
		6	AML with MDS related changes FAB type AML4	46,XY,add(7)(q31)[15]/46,XY[1].ish der(7)t(1;7)(q32;q31) (WCP7+,WCP1+)	0.5	Death from AML /no HSCT
Definitive non-malignant SC						
5263	p.[Lys62X]+[Cys84fs]	0.05	Aplastic	No abnormality	10.4	Alive after HSCT
5855	p.[Lys62X]+[Cys84fs]	0.1	Aplastic	No abnormality	0.21	Death / supportive care respiratory distress
5170	p.[Lys62X]+[Cys84fs]	0.4	Hypoplastic	No abnormality	10.3	Alive after HSCT
5512	p.[Lys62X]+[Cys84fs]	0.2	Hypoplastic	No abnormality	8.3	Alive after HSCT
5128	p.[Cys84fs]+[Cys119Arg]	12.2	Hypoplastic	No abnormality	22.1	Alive after HSCT
5184	p.[Lys62X]+[?]	5.9	Hypoplastic with mild dyserythropeisis features	No abnormality	17.1	Alive after HSCT
5589	p.[Cys84fs]+[Glu99fs]	0.1	Hypoplastic with dysgranulopoietic features	No abnormality	1.9	Death / no HSCT
5770	p.[Cys84fs]+[exon 2 deletion]	0.73	Normally rich bone marrow no blasts Granulopoietic maturation arrest	No abnormality	0.37	Death / no HSCT

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Transient then definitive SC						
5098	p.[Cys84fs]+c.[624+1G>C]	8	No BM smear	Not done	17.2	Definitive not clonal SC 7/9 years after
		15.6	Hypoplastic	No abnormality	9.67	Alive after HSCT
Transient SC						
5154	p.[Lys62X]+[Cys84fs]	1.6	No BM smear	Not done	13.8	Stable situation
5139	p.[Lys62X]+[Cys84fs]	0.4	Hypoplastic	no abnormality	16.4	Stable situation
5171	p.[Lys62X]+[Cys84fs]	6.5	No BM smear	Not done	8.3	Stable situation
5207	p.[Lys62X]+[Cys84fs]	0.28	Hypoplastic	No abnormality	19.3	Stable situation
5504	p.[Lys62X]+[Lys148Thr]	0.9	Dysmyelopoietic features hemophagocytosis	No abnormality	8.4	Stable situation
5777	p.[Cys84fs]+[Pro6Leu]	3.4	No BM smear after CBC normalization hypoplastic with dysgranulopoietic features + neutrophil phagocytosis	Not done	4.3	Stable situation
5180	p.[Lys62X]+[Cys84fs]	0.2	Erythroblastopenia	No abnormally	20	Stable situation
5254	p.[Cys84fs]+[Cys119Tyr]	0.4	No BM smear	Not done	49	Stable situation
5620	p.[Lys62X]+[Cys84fs]	0.13	No BM smear	Not done	6.31	Stable situation
7011	p.[Lys62X]+[Cys84fs]	0.1	Maturation arrest	No abnormally	0.3	Stable situation
5764	p.[Lys62X]+[Cys84fs]	0.75	Maturation arrest	no abnormality	3.25	Stable situation
Bone marrow cytogenetic clone without SC						
5074	p.[Lys62X]+[Cys84fs]	26.5	Rich mild dysgranulopoiesis and dysmegakaryopoietic	46,XX,del(20)(q11q13)[10]/46,XX[20]	10.7	Stable situation
5321	p.[Lys62X]+[Cys84fs]	5.6	Rich mild dysgranulopoiesis with bilobated nuclei / segmentation defect	46,XY,del(20)(q1?1)[6]/46,XY[28]	3.7	Stable situation
5519	p.[C84fs]+[Arg218Gln]	6.5	Poor mild dysgranulopoiesis with bilobated nuclei / segmentation defect	46,XY,t(16;20)(q24;q11.2)[2]/46,XY,i(7q) [1]/46,XY[17]	7.4	Stable situation
5571	p.[C84fs]+[Arg218X]	13.6	Poor mild dysgranulopoiesis with bilobated nuclei / segmentation defect	46,XY,del(20)(q?)[7]/46,XY[23]	5.3	Stable situation
5670	p.[C84fs]+[Phe57Leu]	3.7	Rich mild dysgranulopoiesis with bilobated nuclei / segmentation defect	isochromosome 7q	1.1	Stable situation
5715	p.[C84fs]+[Gln103fs]	2.8	Rich mild dysgranulopoiesis with bilobated nuclei / segmentation defect	46,XY,del(20)(q1?2)[16]/46,XY[4]	2.14	Stable situation
5579	p.[C84fs]+[exon 2 deletion]	7.56	Rich mild dysgranulopoiesis with bilobated nuclei / segmentation defect	46,XX,?dup(9)(p13)[?6]/46,XX[24] 44,X,-X,add(9)(p22),-13,-14,-14,+2mar[2]/46,XX[18]	4.8	Stable situation
6251	p.[Cys84fs]+[Cys19Thr]	22.5	Rich mild dysgranulopoiesis with bilobated nuclei / segmentation defect	46,XX,i(7)(q10)[12]/46,XX[8]	0.5	Stable situation
5451	p.[Lys62X]+[Cys84fs]	5.5	Poor mild dysgranulopoiesis with bilobated nuclei/ segmentation defect	46,XX,del(20)(q12)[4]/46,XX[29]	6	Stable situation

*HSCT: hematopoietic stem cell transplantation; AML: acute myeloid leukemia; MDS: myelodysplasia; FAB: French American British classification of leukemia; RAEB: refractory anemia with excess blasts; BM: bone marrow; *age at event.*

Online Supplementary Table S2A. Details of allelic changes, including the nucleotide sequence changes and deduced consequences at the protein level. The results are given for the 102 patients belonging to 93 families. Each allele was counted only once per multiplex family.

Location	Nucleotide sequence change	Protein effect	Type of mutation	Number of alleles	Percentage	References
Exon 1	c.13delA	p.Thr5fs	Frameshift mutation	1	< 0.01	This report
Exon 1	c.17C>T	p.Pro6Leu	Missense mutation	1	< 0.01	This report
Exon 1	c.56G>A	p.Arg19Gln	Missense mutation	1	< 0.01	48
Exon 1	c.95 A>G	p.Tyr32Cys	Missense mutation	1	< 0.01	49
Intron 1	c.129-2A>G	p.?	Splice defect	1	< 0.01	This report
Intron 1	c.129-1G>A	p.?	Splice defect	1	< 0.01	This report
Exon 2	c.129-71_140del83	p.?	Splice defect	1	< 0.01	This report
Exon 2	c.164C>A	p.Ser55X	Nonsense mutation	1	< 0.01	This report
Exon 2	c.171T>A	p.Phe57Leu	Missense mutation	1	< 0.01	This report
Exon 2	c.183_184delinsCT	p.Lys62X	Nonsense mutation	58	0.31	2
Exon 2	c.[183_184delinsCT; 258+2T>C]	p.[Lys62X;Cys84fs]	Nonsense mutation	6	0.03	2
Exon 2	c.129-?_258+?	p.?	Exon 2 deletion	1	< 0.01	This report
Intron 2	c.258+1G>A	p.Cys84fs	Splice defect	1	< 0.01	2
Intron 2	c.258+2T>C	p.Cys84fs	Splice defect	90	0.49	2
Exon 3	c.279_284del	p.Gln94_Val95del	In-frame deletion	1	< 0.01	48
Exon 3	c.297_300delAAGA	p.Glu99fs	Frameshift mutation	2	0.01	50
Exon 3	c.307_308delCA	p.Gln103fs	Missense mutation	1	< 0.01	49
Exon 3	c.355T>C	p.Cys119Arg	Missense mutation	1	< 0.01	This report
Exon 3	c.356G>A	p.Cys119Tyr	Missense mutation	3	0.02	This report
Exon 3	c.385A>G	p.Thr129Ala	Missense mutation	1	< 0.01	This report
Exon 3	c.443A>C	p.Lys148Thr	Missense mutation	1	< 0.01	48
Exon 3	c.453A>C	p.Lys151Asn	Missense mutation	1	< 0.01	This report
Exon 3	c.461C>T	p.Ala154Val	Missense mutation	2	0.01	This report
Intron 3	c.460-1G>A	p.?	Splice defect	1	< 0.01	48
Exon 4	c.506G>T	p.Arg169Leu	Missense mutation	2	0.01	This report
Intron 4	c.624+1G>C	p.?	Splice defect	1	< 0.01	48
Exon 5	c.652C>T	p.Arg218X	Nonsense mutation	1	< 0.01	51
Exon 5	c.653G>A	p.Arg218Gln	Missense mutation	1	< 0.01	This report
			Undetermined mutation*	2	0.01	
				186		

**In two patients with a documented SBDS phenotype, only one heterozygous SBDS mutation was found.*

Online Supplementary Table S2B. Distribution of the genotypes among the 93 affected families, classified by the consequences of allelic changes.

Genotype	Occurrence	Percentage
p.[Cys84fs]+[Lys62X]	56	62
p.[Cys84fs]+[Lys62X;Cys84fs]	6	6.5
p.[Cys84fs]+[Cys84fs]	1	1
p.[Cys84fs]+[nonsense, frameshift mutation]	8	9
p.[Cys84fs]+[splice defect]	5	5
p.[Cys84fs]+[missense mutation]	12	13
p.[Cys84fs]+[in-frame deletion]	1	1
p.[Lys62X]+[missense mutation]	1	1
p.[Lys62X]+[undetermined mutation]	2	1
p.[Ala154Val]+[Ala154Val]	1	1
		93

Online Supplementary Table S3. Main clinical features of the ten pairs of siblings. All the patients carried the p.[Lys62X]+[Cys84fs] genotype, except for two families, one* with the p.[C84fs]+[Pro6Leu] genotype and one** with p.[Cys84fs]+[large deletion]. The concordance for SC among siblings is shown in the right-hand column; major hematologic events and morphological and developmental features are also shown.

UPN	Sex	Age at diagnosis (years)	Age at last follow up / vital status + cause of death	Severe cytopenia (age)	Major gastro intestinal complications	Major developmental impairment	Bone complications	Heart abnormalities	Baseline ANC median x10^9/L	Baseline platelets median x10^9/L	Concordance for SC
5073	M	0.29	33.7 D (AML)	Yes clonal (MDS)	No	No	No	Yes (aortic coarctation)	0.510	152	No
5074	F	23	39 L – mother of 3 children	No (but isolated transient del 20q)	No	No	No	No	0.768	180	
5616	F	0.73	1.3 D (sepsis during measles)	No	Yes	No	No	No	0.215	54	Yes both with severe expression but AML in only one
5617	F	0.02	2,3 D (AML)	Yes AML like (2.1)	No	No	No	No	1.040	_	
5438*	M*	0.9	2.5 L	No	No	No	No	No	0.595	275	Yes
5439*	M*	0.9	2.3 L	No	No	No	No	No	0.660	258	
5171	M	2.2	11.9 L	No	No	No	No	No	0.574	261	No
5170	M	0.3	9.7 L	Yes SC not clonal	Yes	Yes	No	No	0.392	125	
5062	F	0.4	30L	No	No	No	No	No	0.886	166	Yes
5063	F	1.05	38 L – mother of two children	No	No	No	No	No	0.566	154	
5029	M	0.13	17 L	No	No	Yes	Yes	No	0.864	341	Yes
5030	M	0.54	12 L	No	No	No	No	No	0.784	191	
5769	F	0.22	0.7 D sepsis	No	No	No	No	No	0.694	401	No (severe expression in 2/3)
5570	F	0.06	1.1 D sepsis	Yes	No	Yes, severe seizure	No	Cardiomyopathy	0.825	459	
5579	F	0.15	8.4 L	No	No	No	No	No	0.595	275	
5777	M	7.6	8.6 L	No	No	No	No	No	0.885	186	Yes
5778	M	4.5	5.6 L	No	No	No	No	No	1.577	244	

*UPN: unique patient number; M: male; F: female; L: living; D: dead; ANC: absolute neutrophil count; AML: acute myeloid leukemia; SC: severe cytopenia. *monozygotic twins.*